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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/813760
Filing Date: March 31, 2004
Appellant(s): Bernstein, Joel E.

Joel E., Bernstein
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 04, 2010 appealing from the Office action mailed August 06, 2009 and the Advisory Action mailed October 05, 2009.

(1) Real Party in Interest
A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences is contained in the brief. Appellant states that appellant is not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct

This appeal involves claims 1-3, 5-9 and 11-15.

(4) Status of Amendments

An amendment after final has been filed September 04, 2009 and entered accordingly as indicated in the Advisory Action issued October 05, 2009.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matters contained in the brief is correct.

(6) Grounds of Rejection to Be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal in the brief is correct.

(7) Claims Appendix Grouping of Claims

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Appendix

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

General Pharmacology, Vol. 28, No. 2, pp. 257-263 Kroger et al. 1997

USP 5,478,815 Ogata et al. 12-1995

USP 4,526,788	Murdock et al.	07-1985

The following is a listing of the supporting evidences (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

USP 4,314,989	Rosen	02-1982
US 2009/0124606	Gacsalyi et al.	05-2009
USP 6,733,797	Summers	05-2004
USP 6,048,846	Cochran	04-2000
USP 4,581,348	Schawartz et al.	04-1986
USP 4,401,657	Kashiwabara et al.	08-1983
USP 4,837,239	Benjamin et al.	06-1989
Eksp. Klin Farmacol., abstract, 60(2):68-71 Kegon'kova et al. 1997		
USP 5,994,410	Chiang et al.	11-1999
USP 6,881,401	Yu et al.	04-2005
Conversion Factor Freireich EJ. et al. 1966		
USP 7,557,142	Campbell	07-2009
USP 5,284,861	Lobisch et al.	02-1994
USP 5,059,592	Yokota et al.	10-1991
USP 6,465,511	Kazmierski et al.	10-2002
USP 3,983,250	Abdallah et al.	09-1976

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-3, 5-9 and 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroger et al. (Gen. Pharmac., Vol. 28, No. 2, pp. 257-263, 1997), and further in view of Ogata et al. (USP 5478815) and Murdock (USP 4526788). This rejection is set forth in prior Office Action, mailed August 06, 2009.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-3, 5-9 and 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroger et al. (Gen. Pharmac., Vol. 28, No. 2, pp. 257-263, 1997), and further in view of Ogata et al. (USP 5478815) and Murdock (USP 4526788).

Kroger teaches use of combination of nicotinamide (12.5mg/kg IP or from 25 mg/kg to 100mg/kg IP) and methionine (12.5mg/kg IP or from 25 mg/kg to 100mg/kg IP) in decreasing hepatotoxicity induced by the hepatotoxic compound such as 500mg/kg of acetaminophen (abstract; Figure 2; Results; Discussion). Kroger teaches that the combination of l-methionine and nicotinamide even at lower dose of 12.5mg/kg IP each synergistically results in complete protection from acetaminophen-induced release of GOT and GPT.

Ogata is being provided as a supplemental reference to demonstrate the routine knowledge (in pharmaceutical art) in using intraperitoneal injection as experimental animal testing for the administration of systemic or oral drugs (Examples; column 2, lines 28-31).

Murdock is being provided as a supplemental reference to demonstrate the routine knowledge (in pharmaceutical art) in calculating human dosage based on the interrelationship of dosages for animals of various sizes and species and humans described by Freireich, E. J., et. al., Rep., 50, No. 4, 219-244, May 1966 (column 5, lines 45-51).

Kroger differs from the claimed invention in (i) the preparation of a composition comprising acetaminophen, nicotinamide and methionine in the specific amounts, namely about 80-1000 mg dose of acetaminophen, about 5 mg to about 500 mg dose of methionine and about 10 mg to about 500 mg dose of nicotinamide, per standard dose, (ii) the preparation of said

composition in various dosage forms, namely oral or sterile solutions or suspensions form, more preferably tablets, capsules, caplets, intradermal, subcutaneous, intramuscular, intravenous or intrathecal.

One having ordinary skill in the art would have expected as taught by Kroger that the combination of methionine and nicotinamide would provide protection from acetaminophen-induced liver damage and motivated to make such modification to prepare known hepatotoxic drug such as acetaminophen with nicotinamide and methionine combination in various pharmaceutical dosage forms to accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated dosage form. One having ordinary skill in the art would have expected at the time of the invention was made that the results from Kroger could apply to the development of other modes of administration, for example systemic and/or oral administration. As discussed in preceding comments, it was known at the time of the invention was made that intraperitoneal injection is used as experimental animal testing for the administration of systemic or oral drugs (due to ease of administration compared with other parenteral methods in animal study). Thus, one having ordinary skill in the art has basis for perceiving Kroger's study as constituting recognized animal study with clear relevance to utility systemic and/or oral administration in humans.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Determination of the specific dosage amounts of each ingredient in said composition and/or the specific delivery dosage forms, those of ordinary skill in the art would have been readily optimized effective dosages amounts and/or dosage forms as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose would have been calculated according to body weight, body surface area or organ size. Determination of the appropriate dosage amounts or dosage forms for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed in the above prior art references. For example, the referenced 12.5 mg/kg dose of methionine or nicotinamide in mouse is equivalent to 1.04 mg/kg in human (base on Freireich EJ. Et al., 1966 conversion factor) which falls within the instantly claimed dosage range of either methionine or nicotinmaide. Therefore, the references in combination make obvious the instant invention.

Generally, differences in dosage amounts or dosage forms will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such dosage amounts or dosage forms is critical. Where the general conditions of a claim are disclosed in the prior art, it not inventive to discover the optimum or workable dosage amounts or dosage forms by routine experimentation.

(10) Response to Argument

Appellant's arguments and remarks have been carefully considered, but are not deemed to be persuasive.

In response to Appellants' statement that Kroger'97 injected mice intraperitoneally with a composition of an acetaminophen and methotrexate with combination of nicotinamide and methionine (page 5, paragraph 2), the examiner likes to clarify that Kroger'97 is not a study based on the acetaminophen and methotrexate combination induced hepatotoxicity, rather the study involving the synergistic action of low doses of nicotinamide and N-acetylcysteine or L-methionine in protecting acetaminophen-induced liver damage. As clearly identified in 35 USC 103(a) rejection, Kroger teaches use of combination of nicotinamide (12.5mg/kg IP or from 25 mg/kg to 100mg/kg IP) and methionine (12.5mg/kg IP or from 25 mg/kg to 100mg/kg IP) in decreasing hepatotoxicity induced by the hepatotoxic compound such as 500mg/kg of acetaminophen (abstract; Figure 2; Results; Discussion) and the results of using combination of l-methionine and nicotinamide even at lower dose of 12.5mg/kg IP each synergistically in protecting acetaminophen-induced release of GOT and GPT.

Appellant's argument in the response takes the similar position as the previous argument filed April 09, 2009 and that there are three elements of the pending claims which are not taught by Kroger. Applicant sates:

a. Route of administration – In Kroger, nicotinamide or methionine or their combination are administered intraperitoneally ("IP"). This is a very substantive

difference from the routes of administration claimed in the present application. First, IP is virtually never used in humans[1-2] for two principal reasons: (a) IP provides significantly faster and more substantial blood levels of drugs[1-3] than other routes of administration; and (b) risk of infection and bowel adhesions are unwarranted for use of this route in *humans*[1]. There are no drugs approved for IP administration to humans in North America or Europe.

b. Composition and Method – In Kroger, nicotinamide and/or methionine are administered as separate IP injections, and the acetaminophen and methotrexate are administered orally or by IP respectively at an earlier time point. In contrast, in the compositions cited in the pending application, all components (the hepatotoxic active drug agent and the hepatoprotective agents - nicotinamide, methionine, and folic acid) are provided in the same dosage form and administered together in this dosage form (e.g. capsule, tablet, solution).

c. The dosages of nicotinamide and methionine administered IP for protective effects by Kroger are very substantially greater then those administered orally or by injection (but not IP), in the present application. IP dosages used by Kroger range from 25-100 mg/kg nicotinamide and 50-300 mg/kg methionine when each is given alone, to 12.5 mg/kg of each when they are both administered in separate IP injections. Based on the average body weight for adult Americans[4] the dosage of nicotinamide in the claims of the present application ranges from .11 mg/kg to 5.7 mg/kg for males and from .13 mg/kg to 6.7 mg/kg for females, and the dosage of methionine in claims of the present application ranges from .29 mg/kg to 5.7

This argument is not found persuasive. Contrary to Appellant's argument, there are numerous evidences in the art (either pre- or post-dated art), indicating that intraperitoneal injection (IP) is routinely used in animal testing for the administration of systemic drugs and fluids due to the ease of administration compared with other parenteral or oral methods. For instance, US 4,31,4989 discloses an experimental animal testing for the separate IP administration of acetaminophen and methionine sulfoxide acetaminophen (column 3, line 60 through 26). US'989 contemplates and/or concludes that (non-toxic effective amount of) methionine sulfoxide reduces the hepatotoxic effects of acetaminophen and claims for a pharmaceutical composition comprising acetaminophen in admixture with a non-toxic amount of

methionine sulfoxide, which intended for human use (claims 8-10). Similarly, US 2009/0124606 discloses an experimental animal testing for the IP administration of haloperidol where deramciclane is administered orally (Examples). US'606 contemplates and/or concludes that deramciclane is effective in decreasing or eliminating the extrapyramidal side effects caused by antipsychotic drugs such as haloperidol and claims for a pharmaceutical composition comprising deramciclane and haloperidol, broadly an antipxychotic agent in combination with deramciclane, which is intended for human use (claims 1-16).

As discussed in preceding comments, an experimental animal study using IP administration or IP administration in combination with other modes of administration (e.g., IV and oral) is routinely utilized to study the efficacy of particular drugs (see also "Experimental Method" and claims in US 5284861; column 8, lines 5 through column 10, line 13 and column 6, line 65 through column 7, line 10 in US 7557142 for your references). Thus, one having ordinary skill in the art would have expected as taught by Kroger coupled with the state of art knowledge that methionine and nicotinamide combination would provide protection from acetaminophen-induced liver damage and motivated to make such modification to prepare known hepatotoxic drug such as acetaminophen in mixture with nicotinamide and methionine combination in a pharmaceutically acceptable carrier, including various pharmaceutical dosage forms. One having ordinary skill in the art has basis for perceiving Kroger's study as constituting recognized animal study with clear relevance to utility systemic and/or oral administration in humans.

Again, with respect to the determination of suitable dosage forms, there are general references (see USP 6733797 B1; USP 6048846; USP 4581348; USP 4401657; USP 4837239; Kegon'kova et al., Eksp. Klin Farmakol., 1997, abstract, 1997, 60(2):68-71) indicating that

pharmaceuticals containing nicotinamide and methionine alone or in combination generally may be delivered oral, as well as disclosing benefits to be achieved by oral versus other modes of administration (i.e., parenteral). Therefore, there exist general art accepted motivations for formulating drugs for oral administration. Furthermore, determination of appropriate dosage amounts for treatment of intended purpose involving each of the above mentioned formulation is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the prior art (see also USP 6733797; USP 4581348; USP 6048846). Thus, the examiner maintains the rejection of the record.

In response to appellant's argument that "the dosages of nicotinamide and methionine administered IP for protective effects by Kroger are very substantially greater then those administered orally or by injection…", the examiner recognizes that determination of the specific dosage amounts of each ingredient in said composition and/or the specific delivery dosage forms, those of ordinary skill in the art would have been readily optimized effective dosages amounts and/or dosage forms as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose would have been calculated according to body weight, body surface area or organ size. Determination of the appropriate dosage amounts or dosage forms for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed in the prior art references (see also column

3, lines 5-29 of US 5994410 and column 203, lines 23-54 of US 6881401 for your addition references). For example, the referenced 12.5 mg/kg, 25mg/kg and 50 mg/kg doses of methionine or nicotinamide in mouse is equivalent to 1.04 mg/kg, 2.08 mg/kg and 4.16 mg/kg in human, respectively (based on Freireich EJ. Et al., 1966 conversion factor, see attached PTO 892 form) which falls within the instantly claimed dosage range of either methionine or nicotinmaide. Therefore, the examiner maintains that the references in combination make obvious the instant invention.

In response to the appellant's argument that the unpredictability of animal testing reported in Exhibits D, E, F and H indicates that "results of clinical studies that are the basis fro present claims, are not obvious over animal studies", the examiner recognizes that contrary to the appellant's argument, there are numerous evidences showing in the state of art (see US 4314989, US 7557142, US 5284861, US 5059592, US 5804567, US 6465511, US 3983250, etc…) that data from animal model study is generally sufficient to support therapeutic utility or pharmacological utility for a compound, composition or process. The examiner determines that one having ordinary skill in the art has basis for perceiving Kroger's study as constituting recognized animal study with clear relevance to utility systemic and/or oral administration in humans or animals.

In response to applicant's argument that the examiner neither refuted nor responded to the teaching of Kroger et al. 1999 publication, the examiner likes to point out that applicant has

received an action on the merits for the originally elected invention, Group I along with an acetaminophen as the hepatotixc compound (Response filed 02/28/2007). Accordingly the search and examination have been only extended to an acetaminophen alone in combination with methionine and nicotinmaide. Contrary to the merits of the case, Kroger'99 reference discussed the activity of methionine and/or nicotinamide in reducing essentially the liver toxicity of methotrexate. Although acetaminophen is disclosed in the toxicity study, a lower dose (50mg/kg) utilized in the study is not known to cause hepatotoxicity as seen in the Table 3 (as well as line 3 of the abstract). Kroger'99 discloses that mice were given 50mg/kg acetaminophen, which itself has no effect on the liver. There is no conclusive evidence indicated in Kroger'99 that nicotinamide is non-hepatoprotective at high dosage and that at lower dosage nicotinamide increases liver damage from the acetaminophen. As discussed in preceding comments, the examiner's search and examination have not been extended beyond acetaminiphen. Thus, the examiner has not (fully) considered Kroger'99 reference since it is premature to discuss about non-elected species, methotrexate. Even assuming arguendo that Kroger'99 is relevant to the merits of the case, Table 5 discloses that with increasing NA doses, there is a reduction in GOT and GPT activities. Thus, coupled with the result of Table 4, one having ordinary skill in the art would have perceived that the simultaneous administration of either nicotinamide or methionine or both together would be useful in reducing the liver toxic effect of methotrexate, more broadly other drugs at doses known to be hepatotoxic, e.g., acetaminophen (see last ten lines in column 2 of page 205, under "Discussion" of Kroger'99)

In response to appellant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one having ordinary skilled in the art would have been motivated to combine the references and make modification such that the adverse effects associated with oral niacin such as the niacin flush (column 1, line 56 thru column 2, line 4 of US'827) would be greatly decreased by the delivering of niacin in the topical form of nicotinamide (i.e., methyl nicotinate). Furthermore, one having ordinary skilled in the art would have been motivated to arrive at the claimed invention as taught by US'827 (column 6, lines 11-17 of US'827) such that the delivering of methyl nicotinate would provide advantage ("the nutrients get into the blood stream in their pristine state, unaffected by the hydrochloride acid of the stomach and the digestive tract", see column 6, lines 11-16) over oral or intravenous delivery. As discussed in preceding comments, the examiner determines that applicant has presented no evidence to establish the unexpected or unobvious nature of the claimed invention, and as such, claims 2-3 and 4 are properly rejected under 35 U.S.C. 103.

In response to appellant's argument that "the indication of allowability was withdrawn without explanation in the Office Action dated December 19, 2009", the examiner recognizes that the examiner prematurely indicated the allowability of claims 13-15 without full

consideration of an artisan of ordinary skill in pharmaceutical dosage art . Upon further consideration in light of Kroger'97, Ogata et al and Murdock in combination, the examiner vacated the indication of allowability and issued a new ground(s) of rejection (see O.A. mailed December 19, 2008).

(11) Related Proceedings Appendix

The appellant's statement of related proceedings appendix in the brief is correct. There are no decisions rendered by a court or the Board in any proceeding identified pursuant to paragraph (c) (1) (ii) of this section.

Respectfully submitted,

Brian:bk

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March 16, 2010

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